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EXAMINER	
BROOKS, KRISTIE LATRICE	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/519,008	**Applicant(s)** BELANOFF, JOSEPH K.	
	Examiner KRISTIE L. BROOKS	**Art Unit** 1616	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 February 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *05 June 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4 and 8-19*.
   Claim(s) withdrawn from consideration: *5-7*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/John Pak/
Primary Examiner, Art Unit 1616

Continuation of 11. does NOT place the application in condition for allowance because:

Applicant's arguments are not deemed convincing. Applicant argues that the cortisol levels fall to normal well before interferon-α (IFN-α) associated psychotic symptoms arise. Applicant provided several articles that are suppose to suggest that the increase in cortisol is temporary and that there is a delayed onset of psychotic symptoms associated with IFN-α therapy. This argument is not convincing. As discussed prior to, Applicant is not claiming the treatment of a disease, but ameliorating(e.g. . to improve) the symptoms of psychosis associated with IFN-α therapy. Further, it should be noted that Applicant does not have any claim drawn to cortisol, any level in which cortisol is to be present, any time frame in which the glucocorticoid receptor antagonist is to be administered (e.g. during or after IFN-α therapy), or any specific amount (or dosing regimen) of IFN-α that is to be administered to the patient (see instant claim 1). Scatzberg et al. teach the use of a glucocoticoid receptor antagonist, mifepristone, to treat the symptoms of psychosis resulting from the side effect of a medication. Schatzberg et al. teach that mifepristone works by inhibiting the binding of cortisol to its receptor. Ademmer et al. teach that IFN-α can cause neuropsychiatric symptoms and Shizmu et al. teach that IFN-α causes an increase in cortisol. Thus, it would have been obvious to one of ordinary to try mifepristone in the treatment of pyschotic symptoms caused by IFN-α therapy since IFN-α is known to cause psychiatric symptoms and to cause elevated cortisol levels.

Applicant argues that the symptoms of psychosis is limited and defined in the specification (see page 4 lines 4-20) and cannot be construed to read on all psychiatric conditions. The instant specification refers to psychosis as a "psychiatric symptom, condition or syndrome in its broadest sense….or as a side effect of a medication,e.g. interferon-α" (see page 4 lines 4-20). Schatzberg et al. also defines psychosis and symptoms of psychosis in the same light (see column 6 lines 25-32). The interpretation of psychosis (and symptoms) is extremely broad as described by Applicant and Schatzberg. Thus, one of ordinary skill can reasonably assume that mifepristone is capable of treating symptoms associated with IFN-α therapy and as described in Ademmer.

1.132 declaration

Applicant also provided a 1.132 declaration on February 13, 2009 that discloses Applicant's position that the increase in cortisol is not associated with IFN-α therapy and thus, one would not have been motivated to use the teachings of Schatzberg et al. Applicant also provided seven reference articles in support of Applicant's position. However, the declaration is not persuasive. Furthermore, the reference articles provided by Applicant are not found persuasive and are discussed below.

Applicant argues that Shizmu et al. is following up on the earlier work of Roosth et al. where they report that following injections of IFN-α , cortisol levels increase but return to normal within 24 hours. On page 315, the authors note the phenomenon was transient.

This argument is not persuasive. Again, it should be noted that Applicant does not claim any level in which cortisol is to be present, any time frame in which the glucocorticoid receptor anatagonist is being administered, or any specific amount (or dosing regiment) of IFN-α that is being administered (see instant claim 1). Thus, the claims are broad. Secondly, contrary to what Applicant is arguing, Roosth et al. teach that cortisol levels are increased as weekely doses of interferon were increased (see the abstract, page 312 (Materials and Methods), page 314 and the discussion on page 315). Thus, with continous weekly adminsitration of IFN-α, cortisol levels continue to be elevated. Although Roosth et al. do describe a separate experiment in which the cortisol levels return to normal within 24 hours, this is only after 1 injection of IFN-α. This was a timed experiment to measure when the peak concentration of cortisol occurred in the patients serum after one injection. Thus, Roosth et al. is not a teaching away from the use of IFN-α , but showing a basic pharmacokinetic profile of the drug that describes the plasma concentrations of cortisol over a period of time. It is obvious to one of ordinary skill in the art, that as time progesses, the drug will reach its peak and decrease in value over time. Lastly, Roosth et al. teach that numerous side effects, including neuropsychiatric manifestations have been reported and that it is possible that elevated cortisol levels may account for such behavioral changes (see the last paragraph on page 315). Thus, Roosth et al. do suggest that pyschiatric behavior may be related to increased cortisol levels following adminstration of IFN-α.

Next, Applicant argues that Muller et al. confirms the results of Roosth et al. and Shizmu et al. that IFN-α induced cortisol elevation is transient with maximal levels arising after 5.8 hours.

This argument is not convincing. Muller et al. is directed toward to the short term effects of IFN-α in relation to plasma concentration of ACTH and cortisol. The IFN-α and cortisol levels were measured between 16.00 and 24.00 hours after 1 subcutaneous injection was given at 17.00 hours. In all cases, the cortisol levels were increased. Although, the increase cortisol effect peaked at 5.8 hours and decreased thereafter, this is not a teaching away from the use of IFN-α in the instant claims. This is the basic pharmacokinetic drug profile of IFN-α. It is obvious to one of ordinary skill in the art, that as time progesses, the drug will reach its peak and decrease in value over time. Moreover as stated above, Applicant has not claimed any level in which cortisol is to be present, any time frame in which the glucocorticoid receptor anatgonist is to be administered, or any specific amount of intereferon that is being administered. Thus, the claim is broad and and is open to mifepristone being administered during or after IFN-α therapy, or at any point where inhibition of cortisol is beneficial.

Applicant argues that Gisslinger et al. teach that cortisol levels stabilize and remain normal in patients treated with IFN-α for three weeks. Thus, this is to further establish that the increase in cortisol levels are temoporary.

Applicant's arguments are not persasive. As stated above, Applicant has not claimed any level in which cortisol is to be present, any time frame in which the glucocorticoid receptor antagonist is to be administered, or any specific amount (or dosing regimen) of intereferon that is being administered to the patient. Gisslinger et al. teach that patients that were studied after three weeks of IFN-α at 5x5 million units/week had slightly elevated cortisol plasma levels compared to the baseline day (see Fig. 3 and the second paragraph on page 492). Thus, the cortisol levels were not completely back to normal. Applicant has not stated what levels cortisol must be present to cause psychotic symptoms. Further, there is no specific amount (or dosing regimen) of IFN-α being adminstered in instant claim 1. As shown in Roosth et al., patients who received an increased dose of IFN-α each week over a 7 week period all had increased serum cortisol levels all 6 weeks compared to the placebo (1st week) (see Table 2 in Roosth et al. on page 314). Roosth et al. further suggest that patients

receiving IFN-α therapy experienced side effects, incuding neurophysciatric manifestations, and it is possible that the behavioral changes arise as a result of elevated cortisol levels following adminstration of IFN-α. Thus, Gisslinger et al. is not persuasive to overcome the rejection of record because the patients still had a slightly elevated cortisol level compared to the baseline and also, Roosth et al. teach that increased dosages will increase cortisol level over a 7 week period. Gisslinger et al. only discloses patients receving 5x5 million/week for three weeks. Applicant doesn't define the amount used or the time frame in which IFN-α is being administered in the instant claim. Thus, Gisslinger et al. alone is not enoungh to establish that increased cortisol levels caused by IFN-α would not account for psychotic symptoms.

Applicant further argues that the psychotic symptoms arise, months afer IFN-α therapy. Applicant provides four references, Ex. 4-7. that describe the onset of psychotic symptoms somewhere between 4 and 11 months.

These arguments are not persuasive. Applicant has provided me with 4 case reports that describe patients who have developed psychotic symptoms between 3 and 11 months after IFN-α therapy. However, this is not enough to establish that psychotic symptoms that may develop as a result of IFN-α therapy is not related to an increase in cortisol levels. As stated above, Roosth et al. teach that patients receiving IFN-α therapy experienced side effects, incuding neurophysciatric symptoms, and it is possible that the elevated cortisol levels may account for behavioral changes. And futher, it is well known in the art that each patient will respond differently to a drug or may experience different side effects. As shown in Bozikas et al. (Ex. 4), adverse psychiatric side effects are related to dose, duration of therapy, route of administration (see the first paragrapph on page 136) and also a patients psychiatric and medical history (see Schafer et al, Discussion). Thus, for example, a patient who receives a high dose of IFN-α and therefore higher cortisol levels, may develop pysychiatric symptoms more rapidly than a patient receiving a low dose of IFN-α. There are many factors that may effect when or if a patient may develop symptoms. As shown by Applicant, the 4 patients in the 4 case reports provided developed psychotic symptoms at different times (between 3 and 11 months). Thus, there is no certainty when a pateint may develop symptoms nor is out of the question for patients to develop psychiatric symptoms before 3 months. Further, these four case reports do not constitute a standard for all patients who have received IFN-α therapy and developed psychotic symptoms. Psychosis can emerge during IFN-α therapy and a patients psychiatric status should be monitored during all stages of therapy (see Tamam et al, abstract, Ex. 6).

Summary:

Scatzberg et al. teach the use of a glucocoticoid receptor antagonist, mifepristone, to treat the symptoms of psychosis resulting from the side effect of a medication. Schatzberg et al. teach that mifepristone works by inhibiting the binding of cortisol to its receptor. Ademmer et al. teach that IFN-α can cause neuropsychiatric symptoms and Shizmu et al. teach that IFN-α causes an increase in cortisol. Thus, it would have been obvious to one of ordinary to try mifepristone in the treatment of pyschotic symptoms caused by IFN-α therapy since IFN-α is known to cause psychiatric symptoms and to cause elevated cortisol levels.

The 1.132 declaration and reference articles provided by Applicant in support of the declaration fail to overcome the 103 rejections of record. The reference articles as a whole do not establish that it would not have been obvious to one of ordianry skill in the art to use or try mifepristone during IFN-α therapy and that the increase in cortisol levels is not related to the development of psychiatric symptoms. To the contrary, Roosth et al. suggest that IFN-α does cause neuropsychiatric manifestations, and that it is possible that the elevated cortisol levels may account for behavioral changes.

Further, Applicant does not claim cortisol at all in the claim, any level in which cortisol is to be present, any time frame in which the glucocorticoid receptor antagonist is to be administered (e.g. during or after IFN-α therapy), or any specific amount (or dosing regimen) of IFN-α that is to be administered to the patient (see instant claim 1). Thus, the claim is broad and can be interpreted to read on the instant claims. Therefore, the rejection of record is maintained.